Risk and Resilience: a Multimodal Neuroimaging Integration in Aging and Alzheimer's Disease

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It takes a village! Thank you all!

This work is dedicated to all the memories lost to Alzheimer's Disease and to the enduring caregivers, who live everyday to remember their loved ones. May science, one day, find an answer to this conundrum.

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Summary

Aging alone is associated with a wide range of alterations in brain structure and function as well as age-associated cognitive decline and pathological neurodegeneration. Years of research have shown that brain pathology such as neurofibrillary tangles, amyloid deposition (Aβ), and cerebrovascular pathology contribute to decline of cognitive functions in aging and Alzheimer's Disease (AD). Recent research has pointed out that certain lifestyle factors contribute to the ability to cope with pathology, known as resilience factors, while in contrast, risk factors can accelerate and increase the vulnerability towards cognitive decline and neurodegeneration.

This work explores risk and resilience factors across a diverse spectrum of participants ranging from cognitively intact older adults, to mild cognitive impairment (MCI), and clinical AD with a holistic integration of behavioral measures and multimodal neuroimaging markers. Based on four studies this dissertation investigates the association of AD and cerebrovascular pathology, functional connectivity networks and cognition in a pooled data set of 645 individuals. *Study 1* shows the characterization of cognitive performance across cognitively intact elders and the specific influence of demographic factors such as age, sex, and education on cognition. Using a multimodal approach, *Study 2* disentangles the relationship between amyloid deposition (Aβ) and functional connectivity across the AD spectrum at a global and local level. We found a global positive correspondence and a local detrimental effect of Aβ on connectivity centers, starting at the preclinical phase. *Study 3* focuses on the resilience role of functional connectivity in the face of cerebrovascular pathology. Results demonstrate the mitigating effect of functional connectivity on the impact of white matter lesions on cognition. Finally, *Study 4* investigates the neurobiological underpinnings of psychological risk in healthy and at-AD-risk individuals. We show that the presence of subjective cognitive decline is associated with increased psychological risk, which itself was linked to aberrant functional connectivity in AD target regions and beyond.

In summary, our results shed light on the diverse mechanistic underpinning of functional brain networks, hinting at the complex interplay between the brain's functionality at-rest and the multiple pathological processes. Overall, these findings extend the literature on the resilience and risk factors in the context of healthy aging and AD, while providing a holistic integration of the complex mechanisms at play during the aging process.
Keywords:

Risk, Resilience, Aging, Alzheimer's disease, neuroimaging

Zusammenfassung

Der Alterungsprozess ist mit einem breiten Spektrum von Veränderungen der Gehirnstruktur und -funktion, sowie altersbedingter kognitiver Verschlechterung und pathologischer Neurodegeneration verbunden. Jahrelange Forschungen haben gezeigt, dass Pathologien wie neurofibrilläre Bündel, Amyloid Ablagerungen (Aβ) und zerebrovaskuläre Störungen zur Abnahme der kognitiven Leistungsfähigkeit im Alter und bei der Alzheimer Demenz (AD) beitragen. Jüngste Forschungsergebnisse deuten darauf hin, dass bestimmte Lebensstilfaktoren die Fähigkeit, mit Pathologien umzugehen, fördern. Hierbei handelt es sich um die sogenannten Resilienzfaktoren. Im Gegensatz dazu stehen die Risikofaktoren, welche die Vulnerabilität für kognitive Verschlechterung und Neurodegeneration erhöhen und diese Prozesse beschleunigen können.

Diese Arbeit exploriert Risiko- und Resilienzfaktoren in einem breiten Spektrum von Probanden, von kognitiv normalen älteren Menschen über Personen mit leichter kognitiver Beeinträchtigung bis hin zu Personen mit klinischer AD mittels einer holistischen Integration behavioraler Messungen und Markern multimodaler Neurobildgebung. Basierend auf vier Studien untersucht diese Dissertation die Assoziation von AD und zerebrovaskulärer Störungen, funktioneller Konnektivitätsnetzwerke und Kognition in einem gepoolten Datensatz bestehend aus 645 Individuen. *Studie 1* dient der Charakterisierung der kognitiven Leistungsfähigkeit bei kognitiv intakten älteren Menschen und des spezifischen Einflusses von demografischen Faktoren wie Alter, Geschlecht und Bildung auf die Kognition. Mithilfe eines multimodalen Ansatzes entwirrt *Studie 2* die Beziehung zwischen Aβ und funktioneller Konnektivität über das AD Spektrum auf einem globalen und lokalen Level. Es liefert Evidenz dafür, dass das Fortschreiten der Amyloid Ablagerungen entlang funktioneller Konnektivitätsnetzwerke in präklinischen Stadien beginnt. *Studie 3* konzentriert sich auf die resiliente Rolle funktioneller Konnektivität bei Vorhandensein zerebrovaskulärer Pathologien. Ein abschwächender Effekt der funktionellen Konnektivität auf den Einfluss von Läsionen der weißen Substanz auf die Kognition konnte gezeigt werden. Abschließend untersucht *Studie 4* die neurobiologischen Grundlagen des psychologischen Risikos gesunder Personen und Personen mit erhöhtem Risiko für AD. Das Vorhandensein subjektiver kognitiver Verschlechterungen ist mit einem erhöhten psychologischen Risiko assoziiert, welches mit aberranter funktioneller Konnektivität in AD-relevanten Regionen im Zusammenhang steht.

Zusammenfassend erweitern die Ergebnisse der vorliegenden Dissertation die Literatur zu Resilienz- und Risikofaktoren im Kontext gesunden Alterns und AD, indem sie eine holistische Integration der komplexen Mechanismen während des Alterungsprozesses liefert.

Resilienz- Risikofaktoren, Alterungsprozess, Alzheimer Demenz, Bildgebung

List of Original Studies

Study 1:

Benson, G., de Felipe, J., & Sano, M. (2014). Performance of Spanish-speaking community-dwelling elders in the United States on the Uniform Data Set. Alzheimer's & Dementia, 10(5), S338-S343.

Study 2:

Pasquini*, L., **Benson, G*.,** Grothe, M. J., Utz, L., Myers, N. E., Yakushev, I., ... & Sorg, C. (2017). Individual Correspondence of Amyloid-β and Intrinsic Connectivity in the Posterior Default Mode Network Across Stages of Alzheimer's Disease. Journal of Alzheimer's Disease, 58(3), 763-773.

Study 3:

Benson, G., Hildebrandt, A., Lange, C., Schwarz, C., Köbe, T., Sommer, W., ... & Wirth, M. (2018). Functional connectivity in cognitive control networks mitigates the impact of white matter lesions in the elderly. Alzheimer's research & therapy, 10(1), 109.

Study 4:

Benson,G., Schwarz, C. Sommer, W, Flöel, A. &Wirth, M. Psychological risk associated with aberrant functional connectivity in subjective cognitive decline (In preparation).

List of Abbreviations

ACC:	Anterior Cingulate Cortex
AD:	Alzheimer's disease
APOE:	apolipoprotein
Aβ:	Amyloid beta
BOLD:	blood-oxygen-level-dependent
CR:	cognitive reserve
DMN:	Default Mode Netowork
FLAIR:	Fluid Attenuated Inversion Recovery
fMRI:	functional magnetic resonance imaging
MCI:	Mild Cognitive Impairment
MRI:	magnetic resonance imaging
PET:	positron emission tomography
PCC:	posterior cingulate cortex
SCD:	subjective cognitive decline
SD:	standard deviation
WML:	White matter lesions

1 Theoretical Background

1.1 Introduction

"*The aging brain: the mind is resilient, it's the body that fails.*"[1]

People around the world are living longer, but many are also less healthy lives for longer (Murray et al., 2015). Understanding the science of healthy aging has never been more imperative. Aging alone is associated with a wide range of alterations in brain structure and function, as well as age-associated cognitive decline—all of which contribute to the fact that age is one of the strongest risk factors for neurodegenerative disorders (Hedden & Gabrieli, 2004; Yankner, Lu, & Loerch, 2008). Alzheimer's Disease (AD), the most common form of dementia, is considered an "impeding epidemic" due to the rapidly aging global population and increasing life expectancy rates. By 2050, it is estimated that over 135 million individuals will suffer from dementia if no effective therapies are found (Alzheimer's Disease International, 2015). Thus, not only is it crucial to understand the neurophysiological mechanisms and determinants of brain and cognitive health, but also there is a converging need for a holistic integration of the mechanisms at play in order to understand, treat, and prevent pathological aging.

Recent advances in functional and molecular neuroimaging have facilitated the possibility of tracking brain alteration in structure and function as well as measuring in vivo pathology. Studies have shown that neurofibrillary tangles, amyloid beta (Aβ) deposition, cerebrovascular pathology and neurodegeneration contribute to decline of cognitive functions in aging and AD (Blennow & Zetterberg, 2018; Knopman et al., 2003; Raz & Rodrigue, 2006; Wirth et al., 2013; Yankner et al., 2008). Over the last two decades, the contribution of the neuroimaging field has been of paramount importance and has allowed for two crucial lines of research in aging and AD. First, the development of neuroimaging biomarkers has facilitated the concept of AD as a "continuum," which has lead to the study of an essential preclinical phase of the disease (Jack et al., 2018; Sperling et al., 2011). And second, the presence of increased pathology in cognitively intact older individuals has brought about

[1] Taken from: http://www.nytimes.com/1991/04/16/science/the-aging-brain-the-mind-is-resilient-it-s-the-body-that-fails.html?pagewanted=all

the study of the impact of modifiable lifestyle factors, both resilience (i.e. protective) and risk (i.e. aversive) factors, on age- and disease-related cognitive decline (Baumgart et al., 2015; Jansen et al., 2015). Converging these two lines of research, this works explores risk and resilience mechanisms using a multimodal neuroimaging integration with behavioral measures, while advancing the understanding of the intricate brain mechanisms during aging and AD.

The following sections will provide a theoretical background for the presentation of the research I have conducted. This will be followed by a consolidation of the aims and research questions this dissertation answers along with a brief outline of the studies included. Finally, the overall results are discussed along considering limitations and future research directions.

1.2 General background: Alzheimer's disease continuum

Alzheimer's disease is a neurodegenerative disease characterized by the presence of Aβ aggregations and neurofibrillary tangles (tau) accompanied by neurodegeneration and a gradual and continued pattern of cognitive and functional impairment (Blennow, Leon, & Zetterberg, 2006; Blennow & Zetterberg, 2018). Advances in functional and molecular neuroimaging, which allow in vivo measuring of neuropathology and brain changes, have contributed to the development of established neuroimaging biomarkers (Jack et al., 2018). Evidence from longitudinal studies, genetic-at-risk cohorts, and cognitively intact older individuals suggest that neuropathological changes begin decades before the onset of detectable clinical symptoms (Sperling et al., 2011). This scientific progress has led to the representation of the disease in form of a "continuum".

In 2011, established guidelines were presented to include three stages of the AD: (1) presymptomatic or preclinical Alzheimer's, (2) mild cognitive impairment due to Alzheimer's (MCI), and (3) dementia due to AD (Sperling et al., 2011). The physiopathological cascade of AD encompasses the time between the initial brain changes of AD in a preclinical phase, leading to the prodromal stage of MCI followed by the full symptoms of advanced AD. As advancements in imaging and chemical biomarkers proceeded, guidelines were recently revisited in 2018 for a further refinement of the biological basis of the disease continuum. A research framework was provided to

guide work on biomarkers based on the "**Aβ** deposition, pathologic **T**au and **N**eurodegeneration [AT(N)]" classification system (Jack et al., 2018). Briefly, the following stages of the continuum (Figure 1) are stated for clarity of this work:

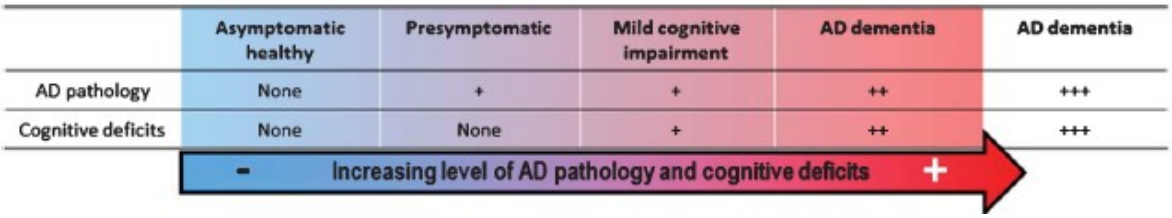

Figure 1. Illustration of the AD continuum from cognitively intact individuals to AD dementia with degree of cognitive deficits and pathology. Image from (Chételat, 2018)

The presymptomatic or preclinical stage of AD (Figure 1) is defined as individuals who have no cognitive or behavioral symptoms, but have evidence of the early brain changes of Alzheimer's (as detected by brain imaging or a bio-marker tests such as Aβ load) (Sperling et al., 2011). Most recently, the field has also progressed towards the earliest stages of the disease to include individuals with subjective cognitive decline (SCD). These individuals have persistent self-experienced cognitive decline in the absence of objective cognitive impairments as measured by normed-standardized cognitive tests (Jessen et al., 2014).

Mild cognitive impairment due to Alzheimer's (MCI) is the stage where mild changes in memory and thinking are noticeable, where cognitive decline is greater than expected for an individuals' age and education level—but not severe enough to impact daily function—along with evidence of AD biomarkers (Albert et al., 2011).

Dementia due to AD is characterized by noticeable memory, thinking, and behavioral symptoms, as well as disruption of daily functions. Criteria diagnosis includes a gradual onset and continuing decline of impairments in social and occupational function in the absence of other psychiatric, neurological or systemic disease causing cognitive deficits (McKhann et al., 2011; Spillantini & Goedert, 2013). It refers to Aβ plaque and pathological tau aggregates, defined in vivo or post-mortem by abnormal biomarkers of Aβ and pathological tau.

1.3 Pathophysiological mechanisms and neuroimaging markers

Despite the major advances in our understanding of AD, the pathophysiological mechanisms of the disease are not yet clear. There are several competing hypotheses concerning the interaction, stages and causes of the pathological hallmarks of AD with the "*amyloid cascade*" and "*tau hypothesis*" still up for debate. Both hypotheses assign a pivotal causal role to the respective pattern of disease pathogenesis. Most current evidence supports the amyloid hypothesis, which proposes that Aβ accumulates (first) and causes the cascade of negative effects such as tau formation, neurodegeneration, cell loss, vascular damage, cognitive decline, ultimately leading to the clinical onset of Alzheimer's Disease (Hardy & Selkoe, 2002; Jack et al., 2018). However, this position is challenged by evidence for tau-related neuronal injury independent of Aβ (Knopman et al., 2013; Spillantini & Goedert, 2013). In parallel, recent neuroimaging studies haven taken into consideration the normal structure and function of the brain to provide evidence for the so-called *network degeneration hypothesis* suggesting that neurodegeneration spreads along brain networks (inter-connected brain regions) which are functionally connected rather than spatially neighboring areas (Jones et al., 2016; Seeley, Crawford, Zhou, Miller, & Greicius, 2009; Zhou, Gennatas, Kramer, Miller, & Seeley, 2012)

Over and above the serial models of causality, the development of multimodal neuroimaging techniques has advanced the understanding of pathology and brain mechanisms that happen in parallel. This allows an understanding of the complimentary and complex brain relationships at play during normal and pathological aging. It is important to note that this work does not involve itself with the causative pathophysiological order of brain changes in cognitive decline and AD. However, for the purpose of simplicity, it accepts a general model of pathology, neuronal degeneration, and cognitive decline outlined in Figure 2, some of which may happen in parallel. The following section will provide a brief overview of the clinical neuroimaging techniques used (illustrated in Figure 2) and their respective measures along with the relevant findings in aging and AD.

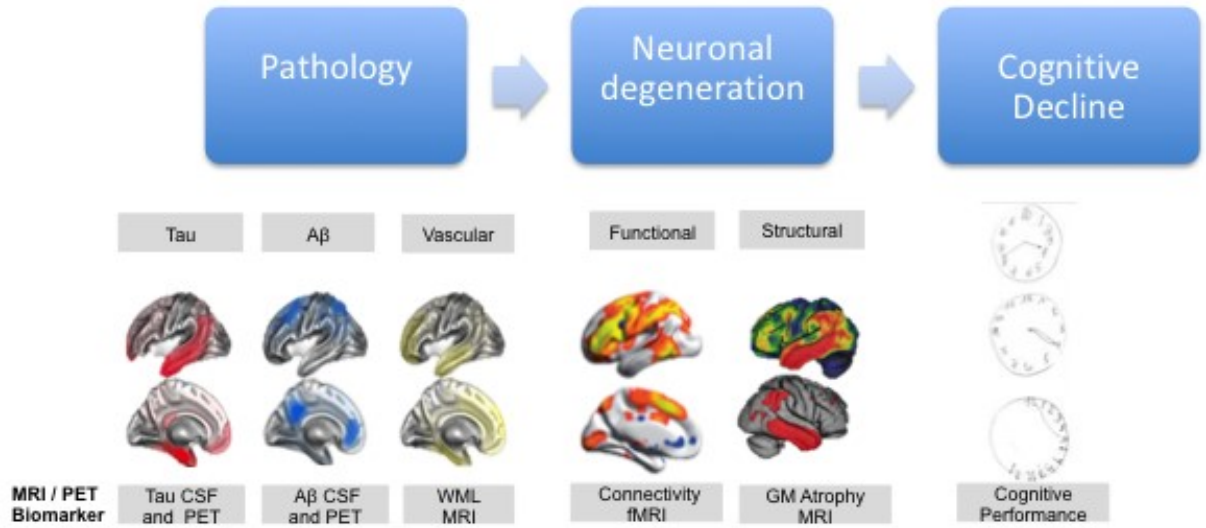

Figure 2. Simplified model of the AD pathogenesis and illustration of neuroimaging biomarkers available for multi-modal integration of the underlying neurobiological processes. Adapted from (Sorg & Grothe, 2015; Villeneuve, Wirth, & La Joie, 2015) **Key:** CSF: cerebrospinal fluid, PET: positron emission tomography, Aβ: amyloid beta, WML: white matter lesions MRI: magnetic resonance imaging, fMRI: functional magnetic resonance imaging GM: gray matter

1.3.1 Amyloid pathology: Position-emission tomography (PET)

The accumulation of the Aβ protein in the brain is a key hallmark characteristic of AD, commonly known as "plaques". The Aβ plaques follow a specific temporal-pattern with initial depositions or accumulation observed in basal portions of the isocortex decades before the onset of symptoms (Braak & Braak, 1991; Jansen et al., 2015). Previously only measurable through cerebrospinal fluid (CSF), advancements in molecular imaging techniques have now allowed for the reliable in vivo imaging of Aβ pathology with positron-emission tomography (PET). The labeling of Aβ pathology in the human brain is preformed using several tracers, the most common of which are Pittsburgh Compound-B (PIB) and Florbetapir (AV-45). Brain regions with high levels of amyloid deposition include lateral and medial parietal areas such as the posterior cingulate cortex, precuneus as well as frontal and temporal brain regions (Grothe & Teipel, 2016). Amyloidosis—the presence of brain Aβ —is consistently reported in almost all subjects with clinical AD, in 50% of subjects with MCI and in 20-30% of cognitively intact older individuals (Blennow et al., 2006; Jansen et al., 2015; Sperling et al., 2011). Paradoxically, individuals with a clinical phenotype of MCI and AD have also reported negative amyloid PET (Doraiswamy et al., 2012; Petersen et al., 2013). These findings

suggest that amyloid-β pathology may be necessary, but not sufficient in isolation, to predict AD trajectory

1.3.2 Atrophy and Lesions: Structural magnetic resonance imaging (MRI)

The MRI is an imaging technique which allows the visualization of detailed internal structures in the human body. In the human brain it can be used to visual gray and white matter, and has been extensively used to explore the atrophy patterns related to normal and pathologic aging (Ibrahim & Osman, 2010). Atrophy can be quantified by estimating changes in cortical thickness and volume via automatic and manual segmentation (Busatto, Diniz, & Zanetti, 2008; Malone et al., 2015). Voxel-based morphometry is an additional technique used to estimate white and grey matter density at a voxel level, as a measure of integrity and atrophy. Typical regions involving first atrophy changes in AD include the hippocampus and entorhinal cortex in the medial temporal lobe (MTL), and the precuneus and posterior cingulate cortex (PCC) in the medial parietal cortex (Buckner et al., 2005).

Volumetric studies suggest an overall shrinkage and thinning of the cortex associated with increased age (Raz & Rodrigue, 2006; Walhovd et al., 2011). In addition to volume changes, pathology in white matter, referred to as “lesions”, is assessed with a special sequence of MRI, namely fluid-attenuated inversion recovery (FLAIR) images. White matter lesions (WML) are considered part of cerebrovascular pathology along with microbleeds and larcunar infarcts. Those WML are common in more than 50 % of the elderly population (Prins & Scheltens, 2015). Increased WML load is associated with worse cognitive performance, and known to affect brain structure (Raz & Rodrigue, 2006). In general, changes structural integrity in both gray and white are consistently reported in both healthy and pathological aging (Jack et al., 2009; Raz & Rodrigue, 2006; Walhovd et al., 2011).

1.3.3 Functional Connectivity: Resting-state functional magnetic resonance (fMRI)

Brain activity can be measured with Functional Magnetic Resonance Imaging (fMRI) via the blood-oxygenation-level-dependent (BOLD) signal (Friston, 1994; Huettel, Song, & McCarthy, 2004). The fMRI technique allows the recording of spontaneous brain activity fluctuations while the individual lie at rest or performing a task in the scanner (Biswal, Zerrin Yetkin, Haughton, & Hyde,

1995). The BOLD signal is essentially reflecting a hemodynamic response, namely the fast transport of glucose and oxygen from cerebral blood to brain tissue in order to support neurotransmitter activity and sustain controlled firing (Huettel, Song, & McCarthy, 2004). Animal electrophysiological recordings provide evidence that local field potentials best predict fMRI responses, indicating that the BOLD signal primarily measures the processing of neuronal information within a brain region(Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001).

In resting-state fMRI methodology, when the brain is at rest, intrinsic brain activity is detected by measuring ongoing fluctuations of the BOLD signal at a slow frequency of about 0.1 Hz (Van Dijk et al., 2010). Synchronized intrinsic BOLD activity of distant brain regions has been used to derived patterns of functional connectivity (i.e. temporal correlations in fMRI data) denominated brain resting-state networks (RNs) (Allen et al., 2011; Smith et al., 2009). Several RNs have been established for different critical functions such as sensorimotor, frontal-parietal, salience, default mode processing(Allen et al., 2011; Fox et al., 2005; Menon & Uddin, 2010). Some of these networks resemble activation maps from task-fMRI studies suggesting that RNs underpin human brain function (Allen et al., 2011).

Resting-state networks

Certain networks, such as the default mode network (DMN), are especially relevant for AD (Buckner, Andrews-Hanna, & Schacter, 2008; Greicius, Srivastava, Reiss, & Menon, 2004; Sperling et al., 2009). In general, the DMN is associated with mental states such as mnemonic processes, planning, and self-referential thinking (Buckner et al., 2008). It is a network known to show first AD related changes (Jones et al., 2015; Sorg et al., 2007; Zhang et al., 2010). Alterations in the DMN are related to cognitive decline and decreases in network connectivity is also seen with higher degree of clinical impairment from MCI to AD (Damoiseaux, Prater, Miller, & Greicius, 2012; Koch et al., 2015).

The Fronto-parietal network (aka. Central Executive) is considered a cognitive control network important for the flexible regulation of activity to other functional networks (Cole, Repovs, &

Anticevic, 2014; Cole, Yarkoni, Repovs, Anticevic, & Braver, 2012). Components of this networks include the lateral prefrontal cortex (LPFC), whose brainwide influence is considered to support processes central to human intelligence (Cole, Yarkoni, Repovs, Anticevic, & Braver, 2012). Also considered a control network is the Salience Network, a brain network anchored in the anterior cingulate cortex (ACC) and anterior insula (Menon, 2015). It is a complex network involved in the integration of input from sensory, emotion and cognitive information (Menon & Uddin, 2010); and considered a dynamic mediator, switching between the DMN and the fronto-parietal network(Bressler & Menon, 2010).

In general, functional connectivity can be studied in different ways: for example, integrity of the networks, the relationships between connectivity and behavior, the analysis of the coherent increase or decrease of connectivity, interconnectivity between network etc. Altogether, these approaches help form the understanding of brain functioning in healthy and pathological aging.

Box 1. Summary Key Findings

- Aβ pathology is a key hallmark of AD related to neurodegeneration and impairment.
- Increase gray matter atrophy is present in normal and pathology aging.
- Decrease of white matter integrity and increase WML load are associated with detrimental effects.
- DMN is a prominent AD relevant network, showing differential connectivity patterns across the Disease Continuum.
- The Fronto-parietal and the Salience network are cognitive control networks important for regulation and healthy brain functioning.

1.4 Resilience

The amount of pathology and atrophy, for the most part, is concurrent with the clinical manifestation of the disease and degree of decline (Knopman et al., 2003; Mormino et al., 2014; Yankner et al., 2008). However, since the first observations of the disconnect between the degree of pathology and cognitive decline, there has been a lot of interest in understanding the mechanisms

underlying this resilience(Crystal et al., 1988; Morris et al., 1996; Stern, 2002). Several concepts have been appointed to the study of what makes individuals robust against aging or disease related pathologies; these include cognitive reserve (CR), brain reserve, brain maintenance, and more general notions such as lifestyle factors, compensation and neuroprotection (Arenaza-Urquijo & Vemuri, 2018; Arenaza-Urquijo, Wirth, & Chételat, 2015; Cabeza et al., 2018; Stern, 2012). These concepts all refer to the hypothetical capacity of the brain (i.e. adaptability, efficiency) of maintaining function in the face of aging, pathology or insult, known to many originally as the CR hypothesis (Stern et al., 2018).

Box. 2 Key Concepts

- Reserve/Resilience: "Heuristic concept that helps explain the individual differences in cognition, function, or clinical status, relative to aging and brain disease." Stern et al., 2018
- There is no direct measurement of reserve, however several lifestyle factors have been used as proxies

Existent evidence highlights that certain lifestyle factors help maintain and protect function as well as delay the effects of pathology. For example, it has been repeatedly shown that educational attainment (Brickman et al., 2011; Stern, Albert, Tang, & Tsai, 1999; Vemuri et al., 2012; Wilson et al., 2004), physical activity (Arenaza-Urquijo et al., 2016; Head et al., 2012; Scarmeas et al., 2003) , cognitive enrichment (Scarmeas, Levy, Tang, Manly, & Stern, 2001; Vemuri et al., 2012; Wirth, Haase, Villeneuve, Vogel, & Jagust, 2014) are protective lifestyle factors that attenuate the detrimental effects of AD and cerebrovascular pathologies. New evidence also expands such protective effects to mental practices such as meditation (Chételat et al., 2017), along with consideration of the influence of certain psychological factors on the classic reserve mechanisms (Bartrés-Faz, Cattaneo, Solana, Tormos, & Pascual-Leone, 2018). Neuroimaging studies have also extended the concept of CR to the level of functional brain mechanisms suggesting that those individuals with high reserve, have brain activation patterns that reflect higher neural efficiency and are thus better able to cope with pathology (Bartrés-Faz & Arenaza-Urquijo, 2011; Barulli & Stern, 2013). However, the neurobiological mechanisms of this resilience remain to be clearly defined.

In general, a recent integration of all the findings in the resilience factors research field proposes a more holistic understanding of the moderating role of lifestyle factors between pathology and cognition, see Figure 3. In the context of AD, lifestyle factors may act both through neuroprotective and compensatory mechanisms, depending on the pathological stage. For example, lifestyle factors may offer a direct neuroprotective effect on pathology in the healthy elderly; while a compensatory (moderating) role takes place once pathology has reached a certain level (Arenaza-Urquijo et al., 2015; Chételat, 2018)

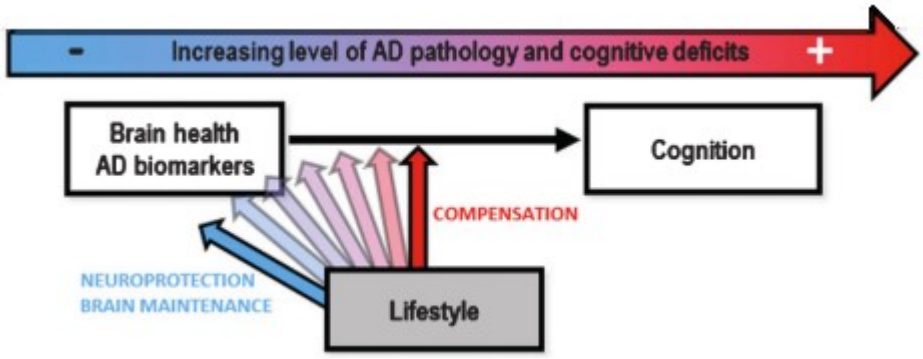

Figure 3. Schematic illustration of the differential expression of resilient mechanisms (neuroprotection and compensation) from cognitively healthy elderly to AD dementia, as presented by (Chételat, 2018).

1.5 Risk factors

The resilience heuristic conceptually allows for the absence or decrease of a protective factor to be referred to as risk factors. The term "risk" is used epidemiologically to describe the future probability of disease as a function of a particular exposure. Non-modifiable risk factors (i.e. genetic background and age) and modifiable lifestyle risk factors (i.e. dietary and psychological factors) have been studied in relation to cognitive impairment and dementia in late life (Hughes & Ganguli, 2009). It is now broadly accepted that cognitive impairment and dementia are associated with both genetic and environmental factors, and their influence on AD pathophysiological mechanisms are included in newer models of the disease (Chételat, 2018; Jack et al., 2018). The most established genetic risk marker for AD is the apolipoprotein E 4 (APOE4) gene (Raber, Huang, & Ashford, 2004). Although the genetic impact is important to consider, these interactions are beyond the scope of this work.

In the absence of effective treatments for AD and the non-modifiable nature of genes, there is considerable interest in the impact of environmental or lifestyle risk factors on cognitive decline in healthy and pathological aging. The list of risk factors is extensive and far-reaching as it may begin as early as in utero, include environmental factors such as head trauma, and health-related behavior (diet/nutrition, tobacco use, etc.) among many others. For an extensive review of all risk factors in late-life cognitive impairment and dementia please refer to Hughes & Ganguli, 2009. In the context of this work, we will focus on the impact of two risk factors, educational attainment and psychological factors.

Educational attainment is the most researched early-life risk factor for cognitive impairment and dementia. Accumulating evidence across cohorts and cultures, suggest that lower educational attainment is consistently found to increase risk of cognitive impairment and dementia(Lopez et al., 2003; Stern et al., 1999; Vemuri et al., 2016; Zhang et al., 1990). The exact mechanisms by which education is related to cognitive impairment is not clearly defined, with several explanations which include: (1) education as a proxy of socio-economic status, which influences other general life health-choices; or (2) its neurobiological basis of increasing long-term neuroprotection through long-term potentiation (Addae, Youssef, & Stone, 2003) among others. As mentioned earlier in the resilience section, educational attainment, along with occupation, premorbid intelligence quotient (IQ), and intellectual engagement are all proxies used in the study of CR and resilient mechanisms (Stern et al., 2018).

Psychological factors have received less attention, but have been consistently associated with increased risk of cognitive decline, MCI risk and dementia (Diniz, Butters, Albert, Dew, & Reynolds, 2013; Hill et al., 2016a; Lopez et al., 2003). Depressive symptomatology, anxiety, stress coping strategies, attitudes towards life and personality are all factors that have the potential to have a detrimental effect on healthy aging (Bierman, Comijs, Jonker, & Beekman, 2007; Escher, Sannemann, & Jessen, 2019; Johansson et al., 2014; Wilson et al., 2006). The concept of "cognitive debt" was recently proposed, as an antonym model of cognitive reserve. According to this concept, psychological factors such as anxiety, depression, repetitive negative thinking, sleep disturbance, are

all factors that deplete resilience against brain disease and may accelerate cognitive decline in aging individuals (Marchant & Howard, 2015).

Evidence on each of these factors supports the association between negative affect and risk for cognitive decline. For example, two major systematic meta-analysis found convincing evidence that history of depression and negative affect significantly increases risk of AD (Diniz et al., 2013; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). Anxiety symptoms are suggested to have an association with cognitive impairment, risk for dementia and higher conversion rate from MCI to AD (Bierman et al., 2007; Sinoff & Werner, 2003; Yochim, Mueller, & Segal, 2013). Likewise, certain personality factors, such as neuroticism, have been linked to increased risk of AD and stepper cognitive decline rates (Pearman, 2004; Snitz et al., 2015). Recent research has started to focus on the neurobiological basis of this risk through the investigation of functional brain changes related to affective factors (Fredericks et al., 2018; Munro et al., 2015; Snitz et al., 2015). In sum, evidence supports the notion of examining psychological factors and their interactions with neuropathological changes across the course of cognitive decline.

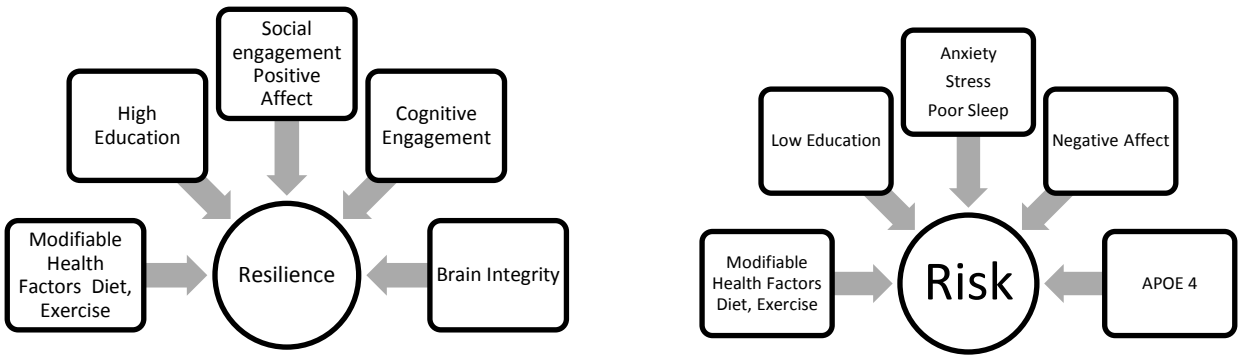

Figure 4. General overview of some of the factors that contribute to resilience and risk in in the context of cognitive decline and AD.

In summary, healthy and pathological aging are accompanied by a complex interaction of neurophysiological mechanism within different brain processes and lifestyle factors, which may increase or reduce the risk of cognitive decline. The previous theoretical overview section has shown the general steps forward in the identification of physiopathological mechanisms across the AD

continuum and the determinants of brain health in aging. There is, however, still a need for further multimodal studies, which help elucidate the links between risk and resilience factors and their effect on brain mechanisms and cognition. Healthy and pathological aging are accompanied by a complex interaction of neurophysiological mechanism within different brain processes and lifestyle factors, which may increase or reduce the risk of cognitive decline.

2 Experimental Aims and Research Questions

This doctoral dissertation seeks to (1) advance the holistic understanding of brain biomarkers (Aβ, functional connectivity, WML) across the AD continuum, (2) further characterizing the neurobiological signature of certain risk and resilience factors and their effect on cognition. The aims of this research project are divided in several objectives pursued through four different studies.

1. In the first study, we started at the most basic level assessing cognitive performance in cognitively intact elders in a sample of Spanish speakers living in the United States. This work was motivated by the lack of descriptive cognitive performance of this sample. At the behavioral level, I examined first hand, **how does age, sex, and education affect cognitive performance in a well-characterized cohort of elders.** Through this framework, I investigated the effects of modifiable (i.e. years of education) and non-modifiable risk factors (i.e. age) on specific neuropsychological assessments.

2. In the second study, we implemented multimodal neuroimaging markers in order to investigate the intricate relationship between brain Aβ burden and functional connectivity. At the level of underlying brain mechanisms, we wanted to know **what is the relationship between amyloid deposition and resting-state functional connectivity across the AD continuum?** We investigated these relationships at a global and local level in the DMN in order to elucidate further evidence for the network degeneration hypothesis.

3. Given that brain pathology and functional connectivity interact differently and lifestyle factors play a role in these relationships, we wanted to investigate these concepts in the context of cerebrovascular pathology. In our third study, we were interested in neurobiological basis of these resilience mechanisms in resting-state network. **Furthermore, we wanted to know if functional connectivity plays a moderating**

role in attenuating the detrimental effect of cerebrovascular pathology on cognition in healthy older adults and individuals with MCI.

4. Lastly, we were interested in investigating psychological risk at the level of functional resting-state networks. In the context of SCD, the earliest stage of the continuum, we wanted to further characterize the affective profile that might posit an additional risk for cognitive decline. We particularly wanted to examine **the neurobiological signature of psychological risk in SCD.**

3 Overview of Empirical Studies

3.1 Study 1

Performance of Spanish-speaking community-dwelling elders in the United States on the Uniform Data Set

Benson, G., de Felipe, J., X. Luo & Sano, M. (2014). Alzheimer's & Dementia, 10(5), S338-S343.

Theoretical background

We investigated the effects of age, gender, and education on cognitive performance in a sample of cognitively intact Spanish speaking elders living in the United States (n=275). This work was motivated by the lack of descriptive of cognitive performance in this sample and was the first descriptive analysis of a multi-center neuropsychological test battery. The Uniform Data Set (UDS) is a standardized clinical and neuropsychological assessment for a multi-center research initiative of the National Alzheimer's Coordinating Center (NACC). Importantly, as a minority group, there was very limited experience with the neuropsychological assessment of aging Spanish speakers living in the United States.

We aimed to present cognitive performance on each cognitive measure described by age and education strata, thereby providing a measure against which to compare cognitive loss and dementia. Further, we wanted to investigate the effects of modifiable and non-modifiable risk factors on specific neuropsychological assessments.

Hypothesis

Given the descriptive nature of this study, it was primarily free of hypotheses. However, we expected demographic features to have the same effects on cognitive performance as reported in an English speaking sample (Weintraub et al., 2009). Namely, worsening of cognitive performance with increased age and better performances associated with increased levels of education.

Major Findings

This work provided the initial cognitive data from clinically normal Spanish speakers in the UDS battery. Participants were notably younger and less educated compared to English-speakers recruited in the same sites. Consistent with previous literature, education and age played a significant role on neuropsychological measures; with higher education and lower ager associated with better performance.

3.2 Study 2

Individual Correspondence of Amyloid-β and Intrinsic Connectivity in the Posterior Default Mode Network Across Stages of Alzheimer's Disease

Pasquini*[*], L., **Benson, G*.,** Grothe, M. J., Utz, L., Myers, N. E., Yakushev, I., ... & Sorg, C. (2017). Journal of Alzheimer's Disease, 58(3), 763-773.

Theoretical background

In AD, a striking overlap exists between the spatial distribution of Aβ pathology and the spatial distribution of functional connectivity. In particular, the aggregation of plaques has been associated with the DMN, a network composed by the medial prefrontal cortex, the medial temporal lobe and includes areas of the medial and lateral parietal cortices as the posterior cingulate and precuneus (Sorg et al., 2007; Sperling et al., 2009). Previous findings have led to the proposal of the network degeneration hypothesis (see section 1.3) which suggest that Aβ accumulation follows the DMN nodes, i.e. along functionally connected rather than spatially neighboring areas (Seeley et al., 2009; Zhou et al., 2012). Previous work from Myers and colleagues reveled two distinct effects of Aβ on functional connectivity when assessing individuals with prodromal AD (Myers et al., 2014). At the global network level, the authors found positive correspondence, with plaque accumulating in areas of

[*] * Equal authorship contribution

high connectivity; while at the local network they revealed a negative relationship, with Aβ plaque load negatively associated with connectivity. They found significant results across heteromodal networks, with the strongest results in the posterior DMN, which is a part of the DMN anchored in the posterior cingulate cortex (PCC).

This study aimed to extend these findings and elucidate the intricate relationship between Aβ and network dysfunction across the temporal progression in the AD continuum in the DMN. Using a cross-sectional design involving multimodal imaging techniques, this study analyzed of a rich data sample (N= 90) including individuals in all stages across the AD continuum.

Hypothesis

The objective was to advance the understanding of neuropathological processes in AD and the relationship within functional connectivity in the DMN. Based on previous findings, we hypothesized a positive global and a negative local spatial correspondence starting at prodromal stages of AD and reaching a plateau at prodromal stages (MCI).

Major Findings

We revealed a positive spatial correlation between patterns of Aβ and functional connectivity across stages of AD, beginning in the preclinical stages. Showing that Aβ accumulates in areas of high connectivity and reaching a plateau at prodromal stages. Local correspondence was negative in network centers, indicating that Aβ reduces connectivity as a function of local Aβ accumulations, starting at preclinical stages and peaking when symptoms appear.

3.3 Study 3

Functional connectivity in cognitive control networks mitigates the impact of white matter lesions in the elderly.

Benson, G., Hildebrandt, A., Lange, C., Schwarz, C., Köbe, T., Sommer, W., ... & Wirth, M. (2018). Alzheimer's research & therapy, 10(1), 109.

Theoretical background

This study focuses on the resilience role of functional connectivity in the face of cerebrovascular pathology. WML are known to affect cognition in aging and is independently associated with an increased risk of dementia (Au et al., 2006; Debette & Markus, 2010; Raz & Rodrigue, 2006). The detrimental effect of WML on cognition has been shown to be attenuated by protective lifestyle factors, providing evidence for the CR hypothesis, which states that individuals with higher reserve are better able to cope with pathological insult (Brickman et al., 2011; Wirth et al., 2014). It has been suggested that individuals with higher CR have brain activation patterns that reflect better neural efficiency, which may help maintain cognitive function in the face of pathology (Barulli & Stern, 2013). Recent works have proposed cognitive control networks, such as the fronto-parietal and the salience network, as neural correlates of CR (Franzmeier, Duering, Weiner, Dichgans, & Ewers, 2017; Serra et al., 2016).However , the neurobiological markers of these resilient mechanisms are unclear in the context of cerebrovascular pathology.

The present study aimed to investigate, whether resting state functional connectivity in cognitive control networks, as a proxy of CR, plays a mitigating role on the detrimental effect of WML on cognition. Functional connectivity was assessed using two approaches: a) global connectivity in the fronto-parietal network, the salience network, and DMN b) local connectivity within each network by extracting regions related to a cognitive reserve proxy (estimated based on education, premorbid IQ, and lifestyle behavior). Latent moderated structural educational modeling examined direct and interactive relationships between WML, functional connectivity and cognition in a sample of 230 non-demented participants.

Hypothesis

We hypothesized a detrimental effect of WML on cognitive functions both memory and executive function. We expected a moderating role of global and local functional connectivity in both the Fronto-parietal and the Salience network. Specifically, we expected that the negative effect of

WML on cognition would be reduced in individuals with higher levels of functional connectivity in both networks.

Major Findings

Increased WML load was associated with worse cognition, in both memory and executive function domains. Higher global functional connectivity in the fronto-parietal network and higher local connectivity between the salience network and the medial frontal cortex significantly attenuated the impact of WML on executive functions.

3.4 Study 4

Psychological risk associated with aberrant functional connectivity in subjective cognitive decline

Benson,G., Schwarz, C. Sommer, W, Flöel, A. &Wirth, M. (In preparation).

Theoretical background

For this last project, we investigated the neurobiological underpinnings of psychological risk in older individuals with and without SCD. The presence of subjective cognitive decline (SCD) is associated with increased risk of AD (Jessen et al., 2014). Increase negative affect, such as anxiety, subclinical depression, rumination and neuroticism are associated with SCD, which in turn is a probable predictor of adverse brain alteration (Fredericks et al., 2018; Hill et al., 2016; Rabin et al., 2015). Recent works have proposed an important role of negative affect in depleting resilience against brain pathology and accelerating cognitive decline in aging individuals (Marchant & Howard, 2015). Functional brain alterations have been demonstrated in SCD, with most studies focusing on the DMN alterations. However, few studies have examined the association of negative affect and functional connectivity in preclinical and prodromal AD. Increased negative affect has been related to functional brain alterations in MCI and early AD (Balthazar, 2013; Munro et al., 2015), and in a recent longitudinal study in healthy older adults, it was related to amyloid positivity and hyperconnectivity in the salience network (Fredericks et al., 2018). There is an essential need to further characterize the

unique psycho-affective profile of SCD and its neurophysiological underpinnings as it could lead to a better understanding of those individuals susceptible to decline.

This study aims to investigate the association of psychological risk with behavioral measures (cognition, cognitive complaints, cognition, and psychological well-being) and functional brain mechanisms in a sample (N=101) of individuals with and without SCD.

Hypothesis

We hypothesized the following: at the behavioral level presence and degree of SCD is related to negative affect, which itself is associated with worse cognitive performance and less psychological well-being. At the neurobiological level, negative affective is related with altered functional connectivity in both the DMN and the Salience Network, particularly in the SCD group.

Major Findings

Individuals with SCD reported higher negative affect, perseverative negative thinking, neuroticism and apathy than those without SCD. A higher degree of cognitive complaints was associated with greater negative affect and less psychological well-being, independently of SCD status. Our resting-state connectivity results indicate that negative affect was related to functional alterations in the DMN and Salience networks, in AD vulnerable brain regions and beyond, across our sample. Importantly, we showed a significant interaction effect of SCD and negative affect showing hyperconnectivity for those with higher negative affect in the SCD group in both networks.

4 Discussion

In the following chapter I will discuss the major findings in light of our research questions and integrate them into the existing literature in the field. Lastly, I will present the limitations of the work and pointing out future research directions finalizing with a general conclusion.

4.1 Summary and evaluation of major findings

The relationships between pathology and resting state networks connectivity

I investigated the intricate role of functional connectivity from resting state networks in the presence of pathology at different stages of the AD continuum and healthy older individuals. Specifically, study 2 investigated the temporal relationship of intrinsic functional connectivity and amyloid pathology across the AD continuum, while Study 3 investigated the protective role of functional connectivity in the presence of cerebrovascular pathology. Both these works shed light on the diverse mechanistic underpinning of functional brain networks, hinting at the complex interplay between the brain's functionality at-rest and the multiple pathological processes.

Complex trajectory of Aβ and functional connectivity correspondence affects Aβ accumulation and connectivity impairments starting at the preclinical stages.

Our results from Study 2 add to a body of literature demonstrating relationships between Aβ burden and resting state functional connectivity (particularly, the DMN) (Buckley et al., 2017; Mormino et al., 2011; Sperling et al., 2009). In line with previous studies, we report a positive global correspondence between Aβ and intrinsic functional connectivity, indicating that Aβ preferentially aggregates in areas of high intrinsic connectivity, specifically the DMN (Myers et al., 2014). Critically, we expand these findings by demonstrating that this global correspondence starts in the preclinical stages in the absence of cognitive symptoms (cognitive intact individuals with Aβ pathology) and reaches a plateau as the disease progresses at the early MCI phase. Our examination of

correspondence between amyloid and functional connectivity at a local level revealed a negative relationship, particularly in the precuneous and posterior cingulate. Indicating that Aβ adversely affects (reduces) connectivity within the centers of the DMN as function of local plaque concentration. Across the continuum, the local deleterious effects of Aβ start at preclinical phases and peaked with the appearance of the first symptoms in early MCI remaining stable.

Our results support the "network degeneration hypothesis" where intrinsic functional connectivity may determine amyloid accumulation patterns (Jones et al., 2016; Seeley et al., 2009; Zhou et al., 2012). Our negative local findings highlight the detrimental effects of Aβ on functional connectivity in network centers, starting at preclinical stages and peaking when symptoms appear. These findings suggest that wherever Aβ accumulation exceeds a certain threshold, accumulated pathology applies a stable long-lasting negative influence in local connectivity. This is in line with previous work, which report a mix of local network disruption due to Aβ in the network "hubs" (central nodes) in the DMN and other network including the Fronto-parietal, suggesting an overall pattern of regional vulnerability (Elman et al., 2016). Furthermore, these findings are in line with results from animal models of AD, which describe a deleterious action of amyloid-β pathology on activity of large-scale circuit function and local network organization (Busche et al., 2008; Palop & Mucke, 2010). Overall our findings shed light on the complex inter-relatedness of these mechanisms and highlight the brain changes that take place already in the preclinical stages of the disease.

Investigating resilience: Functional connectivity from cognitive control networks attenuates the detrimental effects of cerebrovascular pathology

We were interested on neurobiological basis of resilience mechanisms in resting-state network and investigated it in the context of cerebrovascular pathology. In study 3 we found that higher global functional connectivity in Fronto-parietal network and local connectivity between the salience network and medial frontal cortex significantly attenuated the impact of WML on executive functions. These findings suggest that higher connectivity in both cognitive control networks may protect against he detrimental effects of WML. These results are in line with previous findings from Franzmeier and

colleagues which support the protective role of Fronto-parietal network (Franzmeier et al., 2017a). Higher connectivity in this network has been associated with increased CR measures (IQ, education and occupation), and has been known to attenuate the effect of AD pathology on cognition in MCI and AD (Franzmeier et al., 2017b; Franzmeier et al., 2017c). Previous report also support our local findings from the salience network, with similar brain regions (ACC to medial frontal cortex) correlating positively with higher education and preserved cognitive performance(Arenaza-Urquijo et al., 2013). Our finings extend the possible beneficial effects of functional connectivity against WML to include regions from the Fronto-parietal and the Salience network.

The Fronto-parietal and the Salience network are considered crucial for regulation and healthy brain functioning. They support successful cognition, with increased functional hub connectivity linked to better performance(Liu et al., 2017; Menon, 2015). More efficient functional connectivity in these networks may facilitate adaptive connectivity patterns in the presence of neurodegeneration. The detection of resilience mechanisms may be suitable targets for therapeutic interventions to prevent additional cognitive decline. For example, cognitive enhancement techniques has been demonstrated by combining non-invasive brain stimulation over relevant brain areas (Antonenko, Hayek, Netzband, Grittner, & Flöel, 2019). Overall, our findings highlight the crucial role of functional connectivity from cognitive control networks as a neural correlate of resilience mechanisms in older individuals.

Investigating Risk Factors in healthy older adults

The influence and impact of modifiable and non-modifiable risk factors are not only important in the context of AD but also on cognition, mental health and the well-being in healthy aging. In study 1 and 3, I investigated the effect of certain modifiable and non-modifiable risk factors on cognitive performance and the neurobiological signature of psychological risk in healthy older population.

Age and Education have an effect on cognitive performance in healthy older Spanish speakers living in the US

Study 1 presents the performance on neuropsychological test battery from well-characterized cognitively intact older Hispanics living in the US. The limited experience with this cohort in research

has led to a gap in knowledge for the assessment of cognitive loss and dementia in this population. Our study provided the first assessment of the widely used UDS battery (Weintraub et al., 2009) for the Spanish-speaking cohort; and since its publication, it has been taken into consideration when assessing cognition in this population (Burke, Burgess, & Cadet, 2017; Porto, Russo, & Allegri, 2018; Ray, Sano, Wisnivesky, Wolf, & Federman, 2015). Consistent with the well-document phenomenon, we observed the detrimental effect of low education levels on cognitive performance across all tests (Hughes & Ganguli, 2009; Vemuri et al., 2012; Wilson et al., 2004). Contrary to our expectations, fewer test scores were affected by age, with younger age was associated with better performance in only three assessments (delayed recall, verbal fluency and executive function). Our results represent an important tool for assessing cognition and highlight the importance of taking education and age into consideration when assessing cognitive function in aging. These modifiable and non-modifiable risk factors are well known and studied in the field.

Psychological risk: functional alterations in SCD

A less studied phenomenon is the role and influence of psychological affective factors in the risk of cognitive decline and dementia. In my final study, we assessed psychological risk, measured through negative affect, and its association with functional brain mechanisms in cognitive normal individuals with and without SCD. As to be expected from the literature, individuals with SCD reported higher negative affect, which itself was associated with increased cognitive complaints and lower psychological well-being (Hill et al., 2017, 2016b). Across our entire sample, resting-state connectivity results indicated that negative affect was related to functional alterations in the DMN and SAL networks, in AD vulnerable brain regions (such as the precuneus) and beyond. Crucially, there was a significant interaction effect of SCD status and negative affect showing hyperconnectivity in the SCD group for those with higher negative affect in both networks. These results support the notion that psychological risk compromises brain functions, specifically in SCD, which reveal the importance of considering affective factors in early stages of subjective cognitive decline and aging.

It is important to note that connectivity changes presage the onset of objective cognitive impairments (Buckley et al., 2017). Thus, in the context of the initial "unspecified phase" of SCD, assessing the neurobiological basis of psychological risk might a lead to an identification of those individuals susceptible to further decline. In line with this train of thought, it is interesting that we only found a significant interaction of SCD status and negative affect at the neurobiological level. The functional connectivity alterations in the DMN and the Salience network are in line with previous findings that relate hyperconnectivity to higher affective symptoms in MCI, AD and individuals with positive amyloid biomarkers (Binette et al., 2018; Fredericks et al., 2018). Our study extends this in the concept of SCD and hints at distinct psychological profiles of SCD. It has been proposed that early relative hyperconnectivity may posit a detrimental effect as it may place neurons under metabolic stress, rendering them vulnerable to degeneration (Fornito, Zalesky, & Breakspear, 2015; Jones et al., 2015). Therefore it is important to further study these connectivity alterations in these individuals as they age.

4.2 Limitations and future perspective

The importance of longitudinal design

An important caveat to keep in mind in the interpretation of results is the cross-sectional nature of all four studies; hence no causal inference can be concluded. Few studies have examined risk and resilience factors more than a few years prior to the onset of objective decline and dementia; therefore, the discrimination between a true independent of a risk factor and a prodromal or early symptom becomes blurry. Life-long epidemiologic studies are needed in order to assess the interrelations and true associations of lifestyle factors on healthy and pathological aging (Hughes & Ganguli, 2009). Moreover, longitudinal neuroimaging and randomized controlled studies would help inform the progression and the synergies of the impact of lifestyle factors on brain structure and function. Specifically to our studies, longitudinal follow-up from our participants would allow to refine and confirm our proposed model of correspondence trajectory between Aβ and functional connectivity (Figure 3, Study 2). Regarding the protective role of functional connectivity, we could investigate the trajectories of the neuroprotective effects and examine whether there are non-linear

relationships with increase in cerebrovascular pathologies, as similarly proposed in study 2. Lastly, the longitudinal assessment of individuals with SCD is of most importance, not only for the early diagnosis of AD, but also for general healthy aging. The momentum in the research of risk and resilience factors is growing given the proposed evidence that we could modify the disease course, brain, and mental health by adapting lifestyle choices (Baumgart et al., 2015; Valenzuela et al., 2012).

Sample, markers and proxies

It is important to consider the limitations of a research sample setting. It is known that older participants, who are recruited through advertisements and pass screening criteria, tend to be well educated, resulting in a less heterogeneous sample. It is important to keep in mind such "celling effects" when assessing individual differences as it might compromise the accuracy of the estimation of the general population. Likewise, this posits a challenge in the study of resilient mechanisms as educational attainment plays a role has significant impact on AD biomarker trajectories. This effect has been particularly well-described by Vemuri and colleagues showing the different effects of intellectual enrichment on AD biomarkers and their interaction with genetic risk factors (Vemuri et al., 2016). Altogether this highlights the complex interaction between genetic and environmental factors, which is a major hurdle in the evaluation of behavior and assessment of the independent effects of each factor.

Another challenge of empirically testing resilience is the abstract nature of the concept. Given that there is no direct golden standard measurement of reserve, most studies use different proxies, which can lead to a lack of common ground in interpretations. However, the field is moving in the right direction with recent attempts towards a homogenous and consensual integrations of the terminology, study-designs, and findings (Arenaza-Urquijo & Vemuri, 2018; Cabeza et al., 2018; Stern et al., 2018).

Future research directions and outlook

The field is moving and accepting the multifactorial nature of AD. The contributions and interactions from environmental, genetic, and several pathological processes are part of the holistic

models of the disease despite the challenges (design and analysis-wise) it presents. As specific markers of pathological process become more available, (i.e. tau pathology) and more inexpensive, it will be easier for the multimodal integration and investigation of risk and resilience mechanisms.

Future work should focus on the development of reliable and robust preclinical neuroimaging markers, with the inclusion of an optimal combination of several imaging modalities derived from retrospective and longitudinal studies. Future studies are also needed for the biopsychosocial approach to characterize individuals at the earliest phase of preclinical AD. The integration of psychological risk factors is needed in order to understand the etiological factors influencing the presentation, or lack there, of SCD. As the AD field pushes towards an earlier characterization of the disease, the understanding of trajectories of AD and the opportunities of targeted timely intervention becomes imperative.

4.3 Conclusion

The aim of this thesis was to elucidate risk and resilience mechanisms using a multimodal neuroimaging approach, while advancing the understanding of the intricate brain mechanisms during aging and AD. On the relationship between Aβ pathology and resting-state connectivity, we found a global positive correspondence and a local detrimental effect of Aβ on connectivity centers, starting at the preclinical phase. On the level of neurobiological resilient mechanisms, we demonstrated the protective role of cognitive control networks in the attenuation of the detrimental effects of cerebrovascular pathology on cognition. Lastly, we saw the direct effects of modifiable (education) and non-modifiable (age) risk factors on cognitive performance, and the neurobiological correlations of psychological risk on resting state connectivity in healthy older adults. We contextualized our findings within the holistic model of the AD, where interactions from environmental, genetic, and several pathological processes are taken into consideration in the course and severity of the disease.

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Eidestattliche Erklärung/Declaration

Hiermit erkläre ich, die Dissertation selbstständig und nur unter Verwendung der angegebenen Hilfen und Hilfsmittel angefertigt zu haben.
Ich habe mich anderwärts nicht um einen Doktorgrad beworben und besitze keinen entsprechenden Doktorgrad.
Ich erkläre, dass ich die Dissertation oder Teile davon nicht bereits bei einer anderen wissenschaftlichen Einrichtung eingereicht habe und dass sie dort weder angenommen noch abgelehnt wurde.
Ich erkläre die Kenntnisnahme der dem Verfahren zugrunde liegenden Promotionsordnung der Lebenswissenschaftlichen Fakultät der Humboldt-Universität zu Berlin vom 5. März 2015.
Weiterhin erkläre ich, dass keine Zusammenarbeit mit gewerblichen Promotionsbearbeiterinnen/Promoti onsberatern stattgefunden hat und dass die Grundsätze der Humboldt-Universität zu Berlin zur Sicherung guter wissenschaftlicher Praxis eingehalten wurden.

Declaration:
I hereby declare that I completed the doctoral thesis independently based on the stated resources and aids.
I have not applied for a doctoral degree elsewhere and do not have a corresponding doctoral degree.
I have not submitted the doctoral thesis, or parts of it, to another academic institution and the thesis has not been accepted or rejected.
I declare that I have acknowledged the Doctoral Degree Regulations which underlie the procedure of the Faculty of Life Sciences of Humboldt-Universität zu Berlin, as amended on 5th March 2015.
Furthermore, I declare that no collaboration with commercial doctoral degree supervisors took place, and that the principles of Humboldt-Universität zu Berlin for ensuring good academic practice were abided by.

Berlin, den 30.04.2019

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Gloria Spielmann-Benson

6 Manuscripts (Studies 1-4)

Study 1

Benson, G., de Felipe, J., & Sano, M. (2014). Performance of Spanish-speaking community-dwelling elders in the United States on the Uniform Data Set. Alzheimer's & Dementia, 10(5), S338-S343.

DOI: https://doi.org/10.1016/j.jalz.2013.09.002

Study 2

Pasquini*, L., **Benson, G*.,** Grothe, M. J., Utz, L., Myers, N. E., Yakushev, I., ... & Sorg, C. (2017). Individual Correspondence of Amyloid-β and Intrinsic Connectivity in the Posterior Default Mode Network Across Stages of Alzheimer's Disease. Journal of Alzheimer's Disease, 58(3), 763-773.

DOI: https://doi.org/10.3233/JAD-170096

Study 3

Benson, G., Hildebrandt, A., Lange, C., Schwarz, C., Köbe, T., Sommer, W., ... & Wirth, M. (2018). Functional connectivity in cognitive control networks mitigates the impact of white matter lesions in the elderly. Alzheimer's research & therapy, 10(1), 109.

DOI: https://doi.org/10.1186/s13195-018-0434-3

Study 4

Benson,G., Schwarz, C. Sommer, W, Flöel, A. &Wirth, M. Psychological risk associated with aberrant functional connectivity in subjective cognitive decline (In preparation for Submission).

Psychological risk associated with aberrant functional connectivity in subjective cognitive decline

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ABSTRACT

Background. Subjective cognitive decline (SCD) is consistently associated with negative affect, which, in turn, is a probable predictor of adverse brain alteration. Negative affect may constitute a behavioral profile of psychological risk that potentially increase predisposition to AD. **Aim:** to investigate the association of psychological risk with behavioral measures and functional brain mechanisms in cognitively normal individuals with and without SCD.

Methods Cognitively normal older adults with (n=51) and without (n=50) SCD underwent assessment of behavior, cognition, and functional magnetic resonance imaging. The relationships between psychological risk—measured through a combined score of negative affect—cognition, psychological well-being and functional connectivity were assessed. Functional connectivity was examined in two networks known to be vulnerable to AD, default mode network (DMN) and salience network (SAL), and tested for main effects and modification by SCD status using seed-to-voxel connectivity analysis.

Results Presence and degree of SCD were significantly associated with increased negative affect, which, in turn, was related with lower psychological well-being. Greater negative affect correlated with functional connectivity alterations in the DMN (posterior cingulate cortex to middle frontal gyrus) and in the SAL (anterior cingulate cortex to precuneus) across both groups. Interactive effects show the precuneus and the post central gyrus to be associated with hyper-connectivity, specifically in SCD.

Discussion Presence of SCD in older adults is associated with greater negative affect, which itself correlates with aberrant functional connectivity. Our findings suggest that psychological risk is a critical factor that compromises brain function in SCD and may be a suitable target for intervention in this early phase.

BACKGROUND

Subjective cognitive decline (SCD) is commonly expressed in aging individuals in the absence of objective cognitive impairment. SCD is associated with increased risk for Alzheimer's Disease (AD) and has been recently characterized as the earliest symptomatic stage of preclinical AD [1,2]. Accumulating evidence shows associations of SCD with increased biomarker abnormalities and AD pathology years before the onset of objective cognitive decline [3–6]. However, at this initial "phase", SCD is an unspecific condition with multiple underlying etiologies, with some studies considering non-degenerative causes and overall poor health[7–9].

The presence of SCD is consistently associated with anxiety, subclinical depression, rumination, and neuroticism, a personality trait showing amplified reactivity to negative emotion [10–12]. Importantly, these negative affects are related to increased risk for AD and are a probable predictor of brain alteration and cognitive decline [13–15]. The causal path from SCD to objective cognitive loss remains complex and multifaceted. Recent works have proposed an important role of negative affect in depleting resilience against brain pathology and accelerating cognitive decline in aging individuals [16,17]. According to this concept, negative affect and maladaptive responses may constitute a behavioral profile of psychological risk that potentially increases the predisposition to develop AD. However, the characterization of negative affect and its association to functional brain changes in SCD remains unclear.

Structural and functional brain alterations have been demonstrated in SCD [3,4,18], Previous studies have focused on connectivity alterations in the Default Mode Network (DMN), a network known to show first AD-related changes; with both increase [5] and decrease connectivity alterations reported in SCD [50]. However, few studies have focused on the association of negative affect symptomatology and functional connectivity in preclinical and prodromal AD. Reports show that stronger affective symptoms such as neuroticism, apathy and depression, are related to functional brain alterations in individuals with Mild Cognitive Impairment (MCI) and early AD [19,20]. In a

recent longitudinal study, Fredericks and colleagues [21] revealed that increased negative affect—based on a composite of anxiety, depression, neuroticism, and vulnerability, named "emotional reactivity"—predicted amyloid positivity and was related to increased connectivity in the salience network (SAL) in cognitively normal individuals. There is an essential need to further characterize psychological risk in SCD and its neurophysiological underpinnings as it could lead to a better understanding of those individuals susceptible to further decline [16].

The present study aims to examine the psychological risk profile in SCD and its associations with behavioral measures and functional brain mechanisms. First, we assess relationships between psychological risk (measured through a combined score of negative affects) and objective cognition, cognitive complaints, as well as psychological well-being in older individuals with and without SCD. Second, we examine the association between psychological risk and functional connectivity in two resting state networks, the DMN, and the SAL network. We hypothesized the following: At the behavioral level presence and degree of SCD are related to negative affect, which itself is related to lower cognitive performance and less psychological well-being. At the neurophysiological level, negative affect is related to altered functional connectivity in both resting-state networks, particularly in the SCD group.

METHODS

Participants

Data used in this study were obtained from the ongoing SmartAge trial (ClinicalTrials.gov: NCT03094546) data release (01.06.2018) [22]. At the time of analysis, data from 101 participants, n = 51 individuals with SCD and n=50 without SCD (SCD-), were available. Cognitively normal individuals (60-90 years old) were recruited through health care facilities and advertisements in the general population. SCD was diagnosed using established guidelines [1] that included presence of subjective cognitive complaints for at least 6 months, self-reported associated worries and endorsement to seek medical help due to these concerns. Participants without SCD (SCD-) were included if they denied any subjective cognitive worsening or if such cognitive worsening was considered of no concern. For all participants, screening criteria for normal cognitive performance was measured using the Mini Mental State Examination (MMSE) [23] (score $\geq$ 26), the logical memory subscale total delayed recall [24] and the trail making test A [25] (both scores >-1.5 standard deviation [SD] of age adjusted norms). Exclusion criteria for both groups included deficits in activities of daily living [26] and a Geriatric Depression Scale (GDS) [27]score > 10, as well as severe medical, neurological or psychiatric disease.

All participants underwent assessment of behavior, cognition, and functional magnetic resonance imaging, further details of the study are provided elsewhere [22]. Family History of AD and non-specified dementia was defined within the first-degree family members. Overall, six subjects were excluded from imaging analysis due to incomplete visit (n=1), missing MRI data (n=4), failed quality control procedures (n=1), with the remaining 96 subjects comprising the final sample for imaging analysis (49 SCD, 47 SCD-). The study was approved by the ethics committee of the Charité University Medicine Berlin Germany, and was in accordance with the declaration of Helsinki. All participants provided informed written consent.

Neuropsychological Testing

A battery of neuropsychological tests was administered to all the participants to assess cognitive performance. A global cognitive measure was derived similar to the Preclinical Alzheimer's Cognitive composite (PACC 4). This measure was designed to provide distinctive information about early cognitive decline in cognitive intact individuals [28]. Test scores were z-transformed and averaged to create composite scores from the following test: Total MMSE score [23] , total immediate learning recall from the German version of the Auditory Verbal Learning Test (VLMT) [29], the logical memory total delayed recall [24] and the Digit Symbol substitution test.

Self-reported behavioral measures

Self-reported questionnaires were administered on site and at home. Psycho-affective measures were selected from the questionnaire battery [22]. Depressive affect was assessed through the Geriatric Depression Scale (GDS) short version (15 items) [30]. Rumination was assessed with the 23-item Response Style Questionnaire (RSQ-D), which quantifies the extent to which individuals respond to negative events by focusing on self, symptoms, and distraction [31]. Neuroticism, a personality trait, was assessed using the Big-Five Inventory (BFI) neuroticism score from the10-item questionnaire [32]. Stress Coping was evaluated with the 78-item Stress Coping Style Questionnaire (SVF-78), which assesses the coping style (positive or negative) of an individual's particular way of reacting to stressful situations [33].

Further, we selected the following behavioral measures: The degree of Cognitive complaints was assessed with the 39-item Everyday Cognition Scale (ECOG) with the average score provided by the total amount of answered questions as reported in the established scoring method [34]. Psychological well-being was assessed using the WHO Quality of Life-BREF (WHOQOL-BREF) psychological well-being subscale [35].

Assessment of psychological risk

Motivated by the conceptual relevance proposed by Marchant and Howard [16], we calculated a negative affect composite from the psycho-affective measures selected to best represent the individual's psychological risk. We conducted exploratory factor analysis using a principal

component analysis (PCA) estimation approach and a varimax rotation [36], to explore the relationship among all the psycho-affective measures (Table 1), similar to previous approaches [19,37,38]. The Kaiser–Meyer–Olkin (KMO) measure verified the sampling adequacy for the analysis, KMO=0.70, and Bartlett's test of sphericity X^2 (28)=253.411, P<0.01, indicated that correlations between items were sufficiently large for PCA. Two components had eigenvalues over Kaiser's criterion of 1 and in combination these two factors explained 59.8% of the variance. Table 1 shows the factor loadings after rotation. The first PCA (PC1) was composed of negative coping, neuroticism, GDS, symptom- and self-rumination, and suggests that this component represents negative affect while the second component (PC2) contrasted more positive coping strategies. Given the aim of the study, the resulting factor score from PC1, thereafter referred to as negative affect score, was extracted and used for further analysis with higher scores indicating higher negative affect.

Table 1. Summary of principal component analysis to extract Negative Affect scores for the entire sample

Measures	***Rotated factor loadings***	
	Negative Affect	**Positive Coping**
Symptom Rumination	**0.88**	0.073
Self Rumination	**0.76**	0.35
Neuroticism	**0.62**	−0.50
Negative Coping	**0.831**	−0.13
Geriatric Depression Score	**0.63**	−0.37
Distraction Rum	0.10	**0.84**
Positive Coping	-0.11	**0.82**

Note: factor loadings pertaining to a factor appear in bold.

MRI acquisition

Scans were acquired using a 3 Tesla Magnetom Trio (Tim Trio; Siemens AG, Erlangen, Germany) at the Berlin Center for Advance Neuroimaging (BCAN). T1-weighted images were acquired with magnetization-prepared rapid acquisition gradient-echo (MPRAGE) with the following parameters, repetition time (TR = 1900 ms; TE = 2.52 ms; 192 sagittal slices; size = 1.0×1.0×1.0 mm^3; flip angle = 9°). Functional scans were obtained at rest using T2*-weighted EPI sequence (TR = 2300 ms; TE = 30 ms; 34 slices; size = 3.0×3.0×4.0 mm^3; flip angle = 90°). During the 7-min resting-state scan participants were instructed to keep their eyes closed and not think of anything in particular.

Preprocessing and analysis of resting state functional MRI

The publicly available CONN Functional Connectivity Toolbox version 17C (www.nitrc.org/projects/conn), in conjunction with SPM 12 (Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm) was used to perform all preprocessing steps [39]. In detail, we used the default pre-processing pipeline: raw functional images were slice-time corrected, realigned (motion corrected), and co-registered to each participant's MPRAGE image. Images were then normalized to Montreal Neurological Institute (MNI) standard space and spatially smoothed with an 8-mm Gaussian filter. Identification of outlier scans was performed using Artifact Detection Tools (http://www.nitrc.org/projects/artifact_detect) [39]. Specifically, it regresses out scans as nuisance covariates in the first-level analysis exceeding 3 SD in mean global intensity and frame-to-frame difference exceeding 0.5 mm (combination of translational and rotational displacements).

Resting state images were band-pass filtered (0.008-0.09 Hz) and corrected with the implemented component correction (CompCor) strategy [40], including the removal of white/ cerebrospinal fluid time series, motion and artifact-outlier regressors, to reduce the influence of blood-oxygen level dependent (BOLD) signal unrelated to neural activity. There were no significant differences between the two groups in the number of outlier scans (p=0.84) or mean motion ($p=0.82$).

Functional connectivity assessment

Functional connectivity was assessed in both the DMN and SAL networks. Individual connectivity maps were derived using seed-to-voxel analyses from CONN. First level whole brain correlational maps were generated by extracting the mean resting state BOLD time course for each seed and calculating the Fisher-transformed correlation coefficients with the BOLD time course throughout the whole brain. For each network the following seeds were used: the posterior cingulate cortex (PCC): 1,-61,88 for the DMN and the anterior cingulate cortex (ACC): 0,22,35 for the SAL. As defined in our previous work [41], we chose these seeds, given that they are characterized as core

network hubs[42,43]. Individual connectivity maps were then subjected to voxel-wise second-level analysis.

Statistical methods

Statistical analyses were performed with SPSS software 24.0 (PASW, SPSS; IBM, Armonk, NY) and R (version 3.5.0) [44]. A two-sided significance level of α=0.05 was used. Differences between groups (SCD, SCD-) were first assessed on selected demographic, behavioral measures, psycho affective measures, as well as cognitive measures using t-test for continuous variables and Fisher's exact test for categorical variables.

Next, we examined associations between negative affect score, group status, and behavioral measures. Separate multiple linear regression analyses were conducted to investigate relationships between negative affect (predictor) and cognitive complaints, cognitive performance, as well as psychological well-being (outcome variables) in the total sample. In a second step, these statistical models were adjusted for group status and age. In order to further investigate whether there was a modification of these relationships by SDC status, the interactive term (SCD status × negative affect sore) was added in a third step.

Associations between negative affect and resting-state functional connectivity in the pre-selected resting state networks (DMN and SAL) were conducted using voxel-wise second-level analyses. First, we assessed the main effect of negative affect (predictor) on functional connectivity within these networks in the total sample, as previously done [41,45]. In a second step, these models were adjusted for group status and age. Next, the interaction effect between negative affect and SCD status was conducted at the voxel-wise level to assess group differences. This was done, by adding the interactive term (SCD status × negative affect sore) in a third step as a predictor in the one-way ANCOVA models [39]. Significance threshold was established at $p< 0.05$ false discovery rate (FDR) level-correction for multiple comparison and a voxel-level threshold of $p < 0.005$ [39]. Average individual functional connectivity values were extracted from the significant regions as Z-scores. This

connectivity measure was plotted for visualization and interpretation of the directionality using the R package Jtool (available at : https://cran.r-project.org/web/packages/jtools/).

RESULTS

Demographic

Details of the demographic data are shown in table 1. Participants in both groups did not differ in terms of age, education, sex ratio or cognitive performance. Individuals with SCD reported a higher family history of AD and Dementia and reported higher cognitive complaints than those without SCD.

Importantly, the SCD group significantly differed in 6 of the 9 psycho-affective variables from the SCD- group, that indicate a presence of negative affect (Table 2). Correspondingly, individuals with SCD had a significantly higher negative affect score (combined measure), when compared to SCD-.

	SCD-	**SCD**	***p***
Demographics			
N (*n* Women)	50 (25)	51 (25)	.24
Age (years)	71 (6), 60-85	70 (6),60- 83	.66
Education	16.4 (3.4), 10- 29	16.5 (3.6) 11- 27	.80
Family History of Dementia (%)	14%	54.9%	.01
Cognitive Complaints			
Every Day Cognition Overall	1.3 (.3) 1.0-2.4	1.8 (.5), 1.1-3.6	.00
Every Day Cognition Memory	1.5 (.4), 1.0-2.7	2.3 (.6), 1.3-4.0	.00
Psychological Well-Being Cognition	77.8 (12.1) 45-100	70.3 (11.8) 37.5-95.8	.00
Global Cognition: PACC4	.11 (.63) -1.3- 1.5	-.10 (.72) -2.2- 1.34	.12
Psycho-affective Measures			
Geriatric Depression Scale	0.8 (.8), 0-3	1.9 (1.7), 0-6	.00
RSQ-Self Rumination	10.6 (2.8), 7-19	11.9 (3.1), 7-18	.03
RSQ-Symptom Rumination	11.4 (3.0), 8-20	13.7 (3.9), 8-24	.00
RSQ- Distraction	18.9 (5.4), 8-28	19.8 (4.2), 9-32	.36
Stress Coping Positive	13.1 (2.4), 6.6-21.1	13.2 (2.4), 6.9-18	.48

Stress Coping Negative	8.3 (3.3), 0.8-16.8	10.1 (4.4), 2.3-21	.02
Personality Neuroticism	2.6 (.9) 1.0-5.0	3.1 (1.0) 1-5	.02
Negative Affect Score (combined)	-.35 (.75) -1.8- 1.9	.34 (1.9) -1.7- 2.7	.00

Table 1. Demographics and characteristics, numbers are expressed as mean (standard deviations) and range. Independent sample t-test for continuous variables and chi-square test for categorical, Bonferroni corrected. Key: *PACC*4 Preclincal Alzheimer's Cognitive Composite

Relationships between negative affect and behavioral measures

Greater negative affect score was associated with more cognitive complaints (*b*=.27; SE= .03 p>. 01 ; CI =.20-.35) and less psychological well-being (*b*=-8.56; SE =.91; p<.01, CI =-10.38 -6.76) in the total sample. Negative affect was not associated with cognitive performance (*b* = -.04; SE= .07; p=.57, ; CI= -.16 .09), and remained after adjusting for age and group. Also, the SCD status had no significant effect on these associations, as none of the interactions (SCD status × negative affect) were significant (p>.05) for either cognitive complaints (F(1,98)= .02; p=.96) , psychological well-being (F= (1,98)=1.69 ; p=.20), nor cognition (F(1,98)=.08 p=.89).

Relationships between negative affect and functional connectivity

Results of the main effect seed-to-voxel analyses across the entire sample (n=96) are shown in Figure 1 and Table 2. In the DMN, a higher negative affect score was significantly related to higher connectivity between the PCC and the middle frontal gyrus. In the SAL, a higher negative affect score was associated with lower connectivity between the ACC and the precuneus and the precentral gyrus. These results remained significant after controlling for SCD status and age. Cluster information is presented in Table 2.

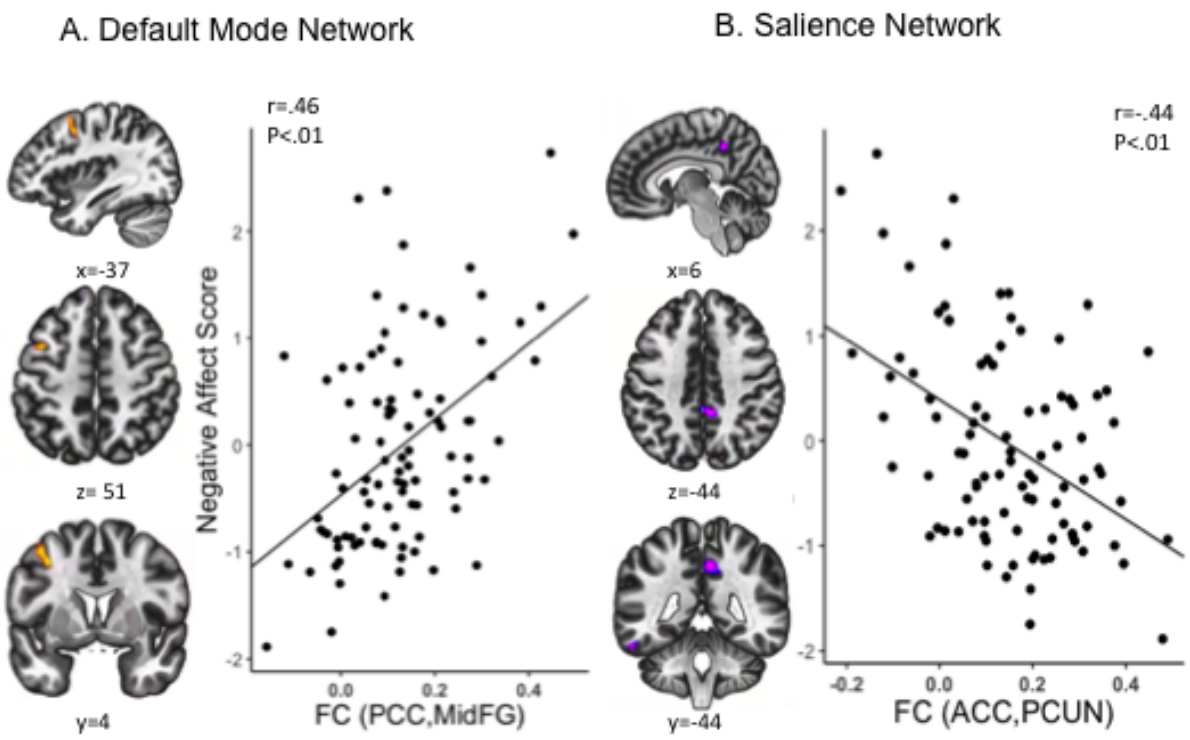

Figure 1. Main effect of negative affect on functional connectivity across all participants. In the DMN (A), higher negative affect was related to higher connectivity between the PCC and in the middle frontal gyrus (MidFG). In the SAL (right side), higher negative affect was related to lower connectivity between the ACC and the precuneus (PCU) as well as the precentral gyrus ($p<.005$; FDR Corrected). The scatterplot illustrates the relationship, negative affect plotted over individual functional connectivity that was extracted from the significant cluster, Pearson's correlation coefficient, $p<.05$ displayed in each graph.

Results of the interaction effect seed-to-voxel analyses are shown in figure 2. In the DMN, brain regions showing a significant interactive effect (SCD status × negative affect) included post central gyrus and the Precuneus for the SAL. In both regions higher negative affect was related to increased functional connectivity for the SCD group, and lower functional connectivity in the SCD- group. These results remained unchanged after controlling for age.

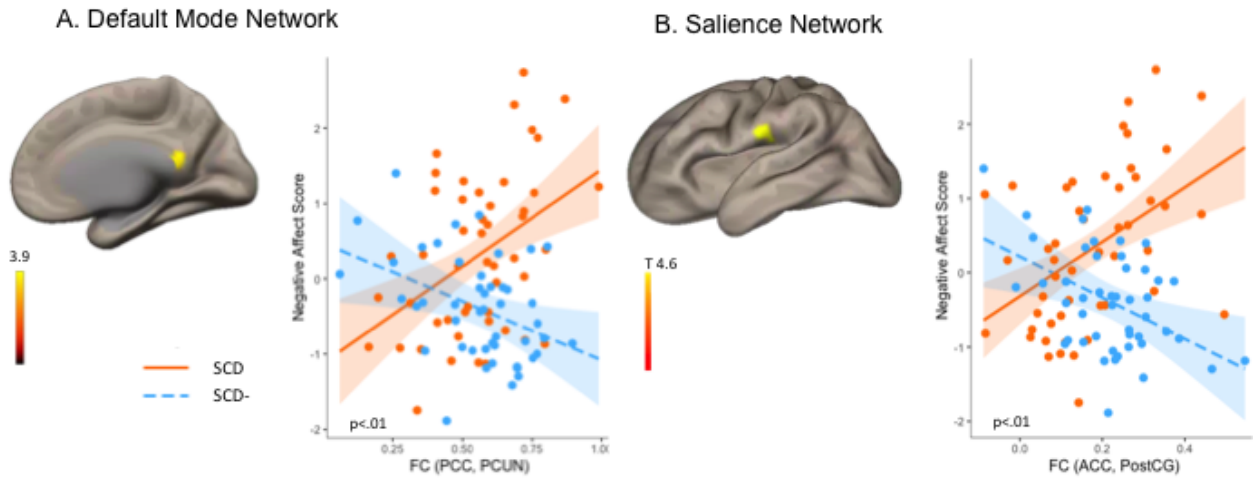

Figure 2. Brain regions showing an interactive effect of SCD status by functional connectivity on negative affect score in the DMN and SAL networks. Brain regions included (A) the cingulate gyrus/precuneus (PCUN) for the DMN and (B) the left postcentral gyrus (PostCG) for the SAL (p<.005 FDR Corrected). In both regions higher negative affect score was related to increased connectivity for the SCD group and lower connectivity for the SCD-. Representations of the interaction effects were illustrated with regression line on scatterplots. Shaded area indicates 95% confidence intervals; p values of the interaction are displayed for each graph.

Regions	**# Voxel**	***p-corrected***	***T***	**Peak MNI Coordinates (x, y z)**		
Default Mode Network seed: PCC						
Middle Frontal Gyrus left	200	.023	4.68	-36	+04	+46
Salience Network seed: ACC						
Precuneus	188	.042	-4.75	+06	-44	+44

Inferior Temporal Gyrus Posterior division left	164	.042	-4.15	-56	-44	-22

Voxel Wise-Interaction Results

Default Mode Network seed: PCC						
Cingulate Gyrus/ Precuneus cortex	134	0.02	3.91	+04	-46	+20
Salience Network seed: ACC						
Postcentral gyrus left / Heschls Gyrus Left	181	.019	4.61	-44	-22	+12

Table 2. Coordinates of the local maxima peaks that showed a significant **main** effect and interactive effect of negative affect. Significant Cluster at $p<0.005$ FDR corrected $p<.05$

DISCUSSION

The present study evaluated psychological risk, measured through negative affect, and its association with functional brain mechanisms in cognitively normal individuals with and without SCD. As to be expected from the literature, individuals with SCD reported higher negative affect, perseverative negative thinking, neuroticism and apathy than those without SCD. Overall, negative affect was associated with increased cognitive complaints and lower psychological well-being, independently of SCD status. Across our sample, resting-state connectivity results indicate that negative affect was related to functional alterations in the DMN and SAL networks, for example in the precuneus—an AD vulnerable brain region—and beyond. Importantly, there was a significant interaction effect of SCD and negative affect showing hyperconnectivity in the SCD group for those with higher negative affect in both networks. Our results support the notion that psychological risk compromises brain functions, specifically in SCD, which reveal the importance of considering affective factors in early stages of cognitive decline and aging.

Our results are consistent with previous findings which show that presence of SCD and the degree of cognitive complaints are associated with increased negative affect and personality factors such as neuroticism, in the absence of objective cognitive impairment [7,9,12]. In addition, our results highlight rumination as part of the psycho-affective characteristics that help form the profile of SCD[46], an important construct of maladaptive reaction to life situations, which should be further studied in SCD[16]. As expected, psychological well-being and cognitive complaints were related to negative affect. The nature of this relationship is in line with previous findings, showing affective symptoms co-occurring in the presence of cognitive complaints; and overall quality of life, particularly psychological well-being, associated with degree of cognitive complaints in older adults[47]. Contrary to our expectation, no associations were found between negative affect and cognitive performance. Although increased psycho-affective symptomology is related to risk for cognitive decline, this association might not be present at this asymptomatic stage. Longitudinal studies might be needed to witness these associations in SCD.

We found that greater psychological risk, as measured through higher negative affect, correlated with functional connectivity alteration in the DMN (posterior cingulate cortex to middle frontal gyrus) and in the SAL (anterior cingulate cortex to precuneus) in our entire sample, a relationship that was independent of age and SCD status. Importantly, these functional associations are seen in AD- vulnerable regions such as the precuneus (a hub normally comprising the DMN), which is related to socio-affective and self-referential thinking[48,49]. Previous studies have focused on connectivity alterations in the DMN, a network known to show first AD-related changes and to be involved in introspection; with both increase [5] and decrease connectivity alterations reported in SCD [50]. Conversely, alteration in the SAL, a system critical for social processing, have been reported across the AD spectrum[51], with connectivity changes related to emotional reactivity in cognitively normal elders [21]. Interestingly, similar alterations in functional connectivity in both the DMN and SAL, extend to other neuropsychiatric disorders such as major depression[52] and obsessive-compulsive disorder[53], suggesting neural circuitry abnormalities implicated in the processing of affective input and emotion internalization [54].

In the present study, we found an interactive effect of psychological risk and SCD status, showing regional hyperconnectivity for the SCD group with increased negative affect in both the precuneus and post-central gyrus (Fig. 2). These results are in line with previous evidence of regional hyperconnectivity associated to increase emotional reactivity [21] and increased neuropsychiatric factors [55] in cognitively normal older adults at risk for AD. Our findings extend this evidence in the context of SCD and hints at a distinct psychological profile of SCD, which exhibits a differential neurobiological correlate, namely, increased relative connectivity. It has been proposed that early relative hyperconnectivity may posit a detrimental effect, as persistent hyperconnectivity in some regions may place neurons under metabolic stress, rendering them vulnerable to degeneration [56,57]. However further longitudinal studies that incorporate psycho-affective measures and biomarkers are needed to inform whether, and to what extent, does psychological risk predicts conversion to dementia in SCD.

Coupled with previous works, our current findings elucidate the association of negative affect and functional brain alterations in SCD. Affective factors are important to examine in the context of SCD given its association with increased risk for AD preceding cognitive decline [14]. Psycho-affective symptoms become more frequent in early or preclinical stages of cognitive dysfunction [58] and are related to differential patterns of AD biomarkers [12]. Therefore identifying mechanism serving psychological risk may help characterize those most susceptible to further decline. Further understanding the distinct profiles of SCD might help identify those who may respond to different interventions (i.e. cognitive behavior therapy) and possibly prevent overall decline.

The interplay of SCD and affective symptoms in the earliest preclinical stages of AD remain complex. Possibly the internalization of the experience of cognitive decline might play an important role in the trajectory of decline. For example, self-experience of cognitive deterioration can precipitate worry about AD, increasing the negative affective symptoms, which in turns exacerbates or accelerates SCD and the overall vulnerability towards AD. Contrarily, certain psycho-affective profiles might just be more sensible to the subtle experience of cognitive decline while already on the path of pathological degeneration course. Although these causal trajectories are beyond the scope of this study, it nevertheless highlights the need for further clarification and supporting evidence.

There are some important limitations to consider. First, our study is somewhat limited by its cross-sectional approach. Further longitudinal studies are needed to capture the value and trajectory of connectivity alterations as subjective decline becomes objective. Second, our measure of psychological risk is a construct derived from our sample and needs further validation. The study of psycho-affective measures as risk factors is heterogeneous in the field, with similar proxies (i.e. “neuropsychiatric burden”, “affective symptoms”) converging comparable results [10]. Some might argue that certain negative affect, like depression, should be treated as confounding factors, however the guidelines of the field of SCD the field suggest against as it provides an incomplete understanding of the expression of SCD[1,2,59]. Lastly, our functional connectivity findings are limited to two networks and should be explored by other functional connectivity measures such as inter-network, degree centrality and other brain networks.

Conclusion

Presence of SCD in older adults is associated with greater psychological risk, which itself correlates with aberrant functional connectivity in AD vulnerable brain regions and beyond. Our findings suggest that psychological risk may compromise brain health and potentiate its adverse impact in SCD. The factor needs to be considered, when investigating suitable intervention strategies in this group.

List of Abbreviations:

AD: Alzheimer's Disease, ANCOVA: analysis of covariance, APOE 4: Apolipoprotein E, DMN: Default Mode Network, KMO: Kaiser–Meyer–Olkin, MCI: Mild Cognitive Impariment MMSE: Mini Mental State Examination, PACC4: Preclincal Alzheimer's Cognitive Composite SAL: Salience Network, SCD: Subjective Cognitive Decline.

Competing interests

The authors have no conflicts of interest to report.

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Supplement

Table 1. Effects of Negative Affect on Cognitive Performance, Cognitive Complaints and Psychological Well-being

	B	SE	**β**	R^2	95 %	P
Negative Affect						
Cognition	-.04	.07	-.06	.04	-.18, .09	.52
Cognitive Complaints	.27	.03	.61	.37	.21,.35	**<.01**
Psychological Well Being	-8.56	.91	-.69	.47	-10.3, -6.7	**<.01**

Associations of Negative Affect (n=100) on Cognition, Cognitive complaints, Psychological Well-being reported as individuals simple linear regressions . Negative *B* values indicate worsening in cognitive performance and psychological well-being